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## Review

## Most antidepressant drugs are safe for patients with epilepsy at therapeutic doses: A review of the evidence

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## ABSTRACT

For a long time, there has been a misconception that all antidepressant drugs have proconvulsant effects. Yet, antidepressants of the selective serotonin reuptake inhibitor (SSRI) and serotonin–norepinephrine reuptake inhibitor (SNRI) families have been not only shown to be safe when used in patients with epilepsy (PWE) but have been found to display antiepileptic properties in animal models of epilepsy. In humans randomized to SSRIs vs. a placebo for the treatment of primary major depressive episodes, the incidence of epileptic seizures was significantly lower among those treated with the antidepressants. On the other hand, SSRIs and SNRIs can display proconvulsant properties at toxic doses. This article reviews the preclinical and clinical data of antiepileptic and proconvulsant properties of these drugs and addresses special considerations to take when prescribing them for PWE.

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## 1. Introduction

Mood and anxiety disorders are the most frequent psychiatric comorbidities in patients with epilepsy (PWE), with lifetime prevalence rates ranging between 30% and 35% [1]. Accordingly, we would expect that antidepressant drugs would be frequently prescribed for these patients, particularly since most of these drugs can yield a therapeutic effect in depressive and anxiety disorders. Yet, such is not the case, and one of the reasons stems from a long-standing misconception held by clinicians that antidepressant drugs cause seizures. This false belief constitutes one of the obstacles in the pharmacologic treatment of mood and anxiety disorders in PWE. Furthermore, data from several animal models of epilepsy have suggested that drugs of the serotonin reuptake inhibitor (SSRI) and tricyclic antidepressant (TCA) families may yield an antiepileptic effect [2,3]. The first part of this review summarizes the data on the impact of antidepressant drugs on seizures in experimental studies and in patients with and without epilepsy. In the second part, we highlight special considerations that need to be taken into account when antidepressants are used in PWE.

## 2. Do antidepressant drugs really have proconvulsant properties?

The “proconvulsant effect” of antidepressant drugs is one of the most misunderstood facts in the practice of medicine, which unfortunately has had dire consequences as it has precluded many physicians from prescribing these psychotropic drugs to PWE. The fact is that, with the

exception of four drugs (see below), the reported seizures associated with antidepressants have occurred when taken at very high doses (e.g., in the setting of overdoses) [4,5]. For example, one study revealed that the minimum citalopram dose associated with seizures was 400 mg [6]. In fact, this observation has been supported experimentally in a study of pilocarpine-induced seizures in rats in which hippocampal perfusion of serotonin (5-HT), up to extracellular concentrations above 900% of baseline, worsened seizures. On the other hand, at concentrations ranging from 80% to 350% of baseline levels, 5HT protected these rats from seizures [7].

The inclusion of seizures as an iatrogenic effect of antidepressants (including SSRIs and SNRIs) in the Physician Desk Reference has perpetuated the concern of prescribing these drugs to PWE since this document does not clarify the conditions under which seizures tend to occur. Furthermore, seizures in patients with a primary mood and anxiety disorder may have resulted from an unidentified medical and/or neurologic condition and yes, from the underlying psychiatric disorder. Indeed, in the last two decades, several population-based studies have suggested that mood and anxiety disorders may be a risk factor for the development of epilepsy [8–11]. Interestingly enough, these data support an observation made by Hippocrates twenty-six centuries ago when he wrote “*melancholics ordinarily become epileptics and epileptics melancholics: what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy*” [12]. In other words, these studies suggest the existence of a bidirectional relation between epilepsy and psychiatric disorders whereby not only are PWE at greater risk of developing these psychiatric disorders, but patients with primary mood and anxiety disorders have a two- to seven-fold higher risk of developing epilepsy. This phenomenon

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has also been described in pediatric patients with epilepsy [13]. Thus, the occurrence of a seizure in a depressed or anxious patient who is being treated with an antidepressant drug may be the expression of the natural course of these psychiatric disorders and not of an iatrogenic effect of the psychotropic drug.

The proconvulsant effect of antidepressant drugs was clarified in a pivotal study by Alper et al., who reviewed data from the Food and Drug Administration Phases II and III clinical regulatory trials of several TCAs, SSRIs, the serotonin–norepinephrine reuptake inhibitor (SNRI) venlafaxine, the  $\alpha 2$  antagonist mirtazapine, and the norepinephrine–dopamine reuptake inhibitor bupropion in patients with primary depression [14]. These investigators compared the incidence of epileptic seizures between patients randomized to the antidepressant drug and to a placebo, and they found a significantly lower seizure incidence among patients assigned to antidepressants (standardized incidence ratio = 0.48, 95% CI, .36–.61). While the seizure incidence was greater in patients randomized to the drug and the placebo than the published incidence of unprovoked seizures in the general population, the seizure incidence was 19-fold higher among patients randomized to the placebo. These data support the increased risk of depressed patients for the development of unprovoked seizures and epilepsy alluded to above and suggest a protective effect of SSRIs and SNRIs. The two antidepressant drugs associated with a higher incidence of seizures than the placebo included clomipramine and bupropion. Separate reports had made a similar observation with respect to bupropion (0.5%–4.8% in a dose-dependent manner) and clomipramine (1%–12.2% in a dose-dependent manner) and had identified amoxapine and maprotiline (incidence: 15.6% in a dose-dependent manner) as two other antidepressant drugs associated with an increased risk of seizures [3]. In summary, with the exception of these four drugs, antidepressant drugs are safe for PWE when used at therapeutic doses.

### 3. Do antidepressant drugs have antiepileptic properties?

Antidepressant drugs, in particular SSRIs and SNRIs, have become the first line of treatment of depression and anxiety disorders in patients with and without epilepsy [15]. Furthermore, antiepileptic properties of SSRIs have been suggested in several experimental studies, which are briefly reviewed below.

The primary pharmacodynamic aim of SSRIs and SNRIs is to increase the synaptic concentration of monoamines, in particular 5HT and norepinephrine (NE). Thus, to demonstrate potential antiepileptic properties, it would be necessary to demonstrate the following: (i) a pathogenic role of serotonergic and/or noradrenergic mechanisms in seizure activity, (ii) a role of monoamines in the antiepileptic effects of antiepileptic drugs (AEDs), and (iii) an antiepileptic effect of SSRIs and SNRIs in several animal models of epilepsy and in double-blind randomized placebo-controlled trials of these drugs in PWE. Of these three conditions, no data are yet available on controlled trials of these drugs in PWE.

#### 3.1. Pathogenic role of monoamines in epilepsy

The pathogenic role of 5HT in epilepsy has been suggested in functional neuroimaging studies using positron emission tomography (PET) in PWE and in experimental animal models of epilepsy.

##### 3.1.1. Neuroimaging studies

Five studies with PET using various 5HT<sub>1A</sub> receptor antagonists in patients with temporal lobe epilepsy demonstrated a decrease of 5HT<sub>1A</sub> binding in several neuroanatomical structures including the epileptogenic hippocampus, amygdala, and anterior cingulate and lateral temporal neocortex (ipsilateral to the seizure focus), as well as in the contralateral hippocampus and in the raphe nuclei [16–20]. Furthermore, reduction in 5HT<sub>1A</sub> receptor binding has also been found in generalized epilepsy in the dorsolateral prefrontal cortex, raphe nuclei,

and hippocampus of 11 patients with juvenile myoclonic epilepsy compared to 11 controls [21].

#### 3.2. Experimental data

A potential pathogenic role of 5HT in epilepsy has been suggested in several animal models of focal and generalized epilepsy. For example, an abnormal serotonergic axon arborization, associated with deficient postsynaptic 5HT<sub>1A</sub> receptor density, has been demonstrated in the hippocampus of genetically epilepsy-prone rats (GEPRs) [22], an animal model of generalized epilepsy in which generalized tonic–clonic seizures are induced with audiogenic stimuli. Furthermore, elevation of 5HT levels with the SSRIs fluoxetine, citalopram, and sertraline resulted in a dose-dependent seizure frequency reduction, which correlated with the extracellular serotonergic thalamic concentration [23], while the 5-HT precursor 5-hydroxytryptophan (5-HTP) has been shown to have anticonvulsant effects when combined with a monoamine oxidase inhibitor (MAOI) [24].

The pathogenic role of 5HT in animal models of focal epilepsy has also been suggested in a model of status epilepticus in male Wistar rats, in which Mazarati et al. demonstrated a decrease of hippocampal 5-HT concentration and turnover as well as a lower 5-HT release from the hippocampus in response to raphe nuclei stimulation [25]. Prendiville et al. demonstrated that fluoxetine prevented seizures when preadministered in the bicuculline (a GABA antagonist) model of focal epilepsy in rats [26], while 5HT agonists have been found to block seizures in other models of focal epilepsy [27].

### 4. Does 5HT mediate the antiepileptic effect of AEDs?

An increase in extracellular 5HT has been found in the GEPR after the administration of several first and second generation AEDs, including phenytoin, carbamazepine, valproic acid, lamotrigine, oxcarbazepine, and zonisamide [24,28–37]. For example, after establishing an anticonvulsant effect of carbamazepine in the GEPR, Yan et al. showed that the addition of 5HT-depleting drugs results in a blockage of this anticonvulsant protection [24]. Likewise, Clinckers et al. investigated the impact of oxcarbazepine (OXC) infusion on the extracellular hippocampal concentration of 5HT and DA in the focal pilocarpine model for limbic seizures [31]. When oxcarbazepine was administered together with verapamil or probenecid (to ensure its passage through the blood–brain barrier), complete seizure remission was obtained, associated with an increase in 5HT and DA extracellular concentrations [32]. Furthermore, SSRIs such as fluoxetine enhance the anticonvulsant effects of phenytoin, carbamazepine, phenobarbital, and valproate in the maximal electroshock seizure model in mice [30].

The antiepileptic effect of 5HT<sub>1A</sub> receptors has been associated with a membrane hyperpolarizing response associated with increased potassium conductance in hippocampal-kindled seizures in cats and in intrahippocampal KA-induced seizures in freely moving rats [38,39]. A recent study has also suggested that the SSRI sertraline could markedly reduce the increase of proinflammatory cytokine expression induced by seizures and convulsant agents and by the inoculation of lipopolysaccharide in the hippocampus including IL-1 $\beta$  and TNF- $\alpha$  mRNA expression [40].

The pharmacologic effect of SSRIs influences other neurotransmitter systems involved in epileptogenesis and seizure propagation such as cholinergic neurons in the septum and glutamatergic neurons in the hippocampus and forebrain regions, where 5HT agonists stimulate acetylcholine and inhibit glutamate release, respectively [41]. Furthermore, stimulation of 5HT<sub>1A</sub> receptors in thalamic relay neurons results in an increase in GABA release and, consequently, a decrease in excitatory activity necessary for spike–wave discharges in absence seizure models [41]. A review by Hamid and Kanner provides a more in-depth discussion of experimental data suggesting an antiepileptic effect of SSRIs [2].

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